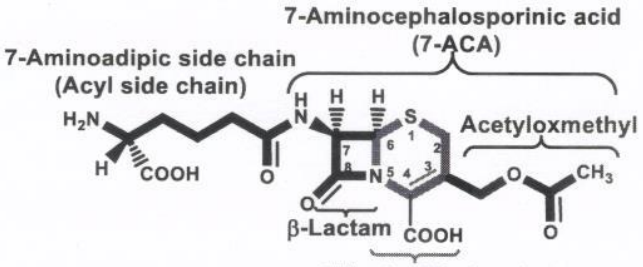
2- Cephalosporins

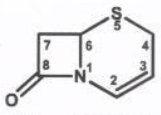
- ✓ The second major group of β-lactam antibiotics.
- ✓ The first cephalosporin (cephalosporin C) was derived from a fungus obtained in the mid-1940s.
- ✓ In cephalosporin, the bicyclic system containing four-membered β-lactam ring fused to a six-membered dihydrothiazine ring*.



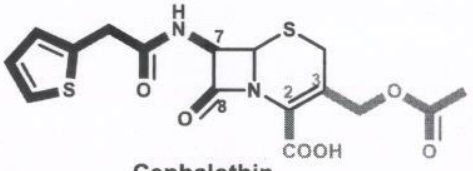
Cephalosporin C

Numbering and Nomenclature

1- According to Chemical Abstract system (bicyclic system)



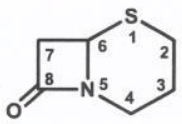
5 -Thia-1-azabicyclo[4.2.0]oct-2-ene-8-one



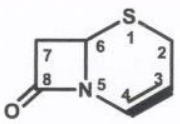
Cephalothin

3-[(Acetoxy)methyl]-8-oxo-7-[(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

2- As Cephem derivative



Cepham

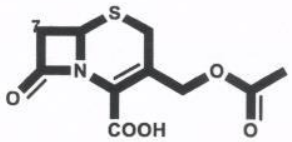


3-Cephem or Δ^3- Cephem

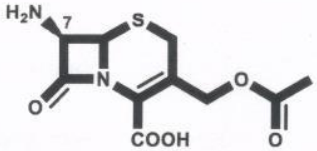
Cephalothin

3-[(Acetyloxy)methyl]-7-[(2-thienyl)acetamido]-3-cephem-4-carboxylic acid

3- As Cephalosporanic acid derivative: It applies only to derivatives having a 3-acetoxymethyl group.



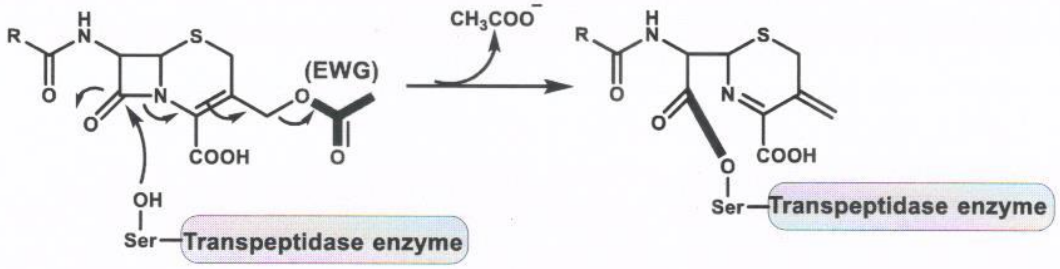
Cephalosporanic acid



7-Aminocephalosporanic acid (7-ACA)

Molecular Mode of Action

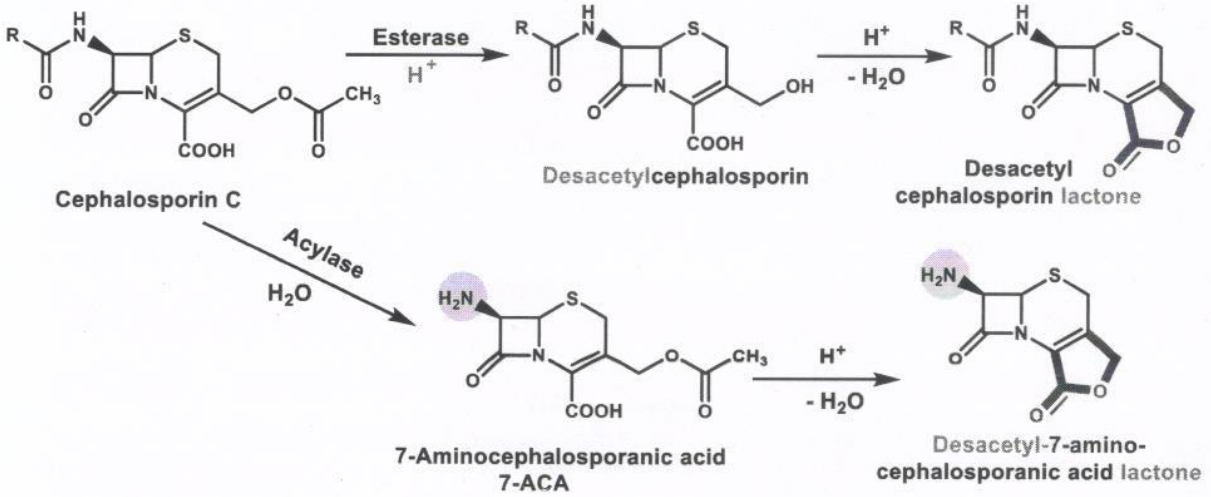
- ✓ The cephalosporins act in a manner similar to that of the penicillins by binding to the penicillin-binding proteins (PBPs) so prevent the PBPs from forming the cross-linkages between the peptidoglycan layers that make up the bacterial cell → cell lysis.



Chemical and enzymatic degradation

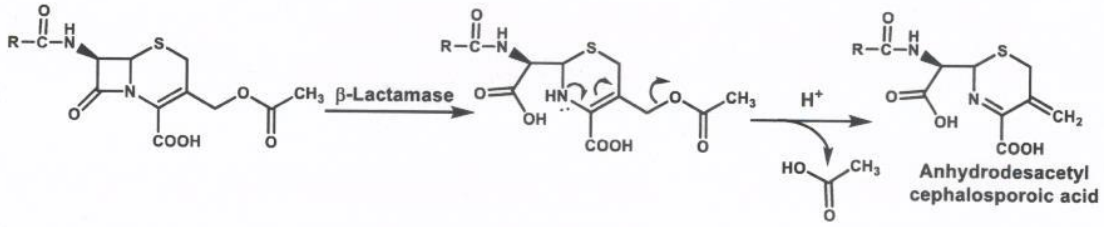
1- Effect of acid, esterase and acylase enzymes

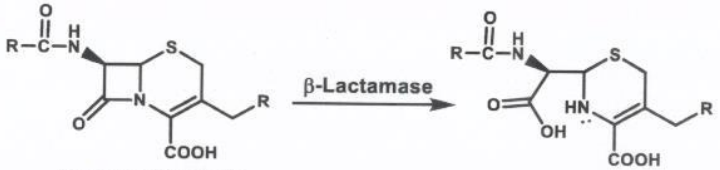
- ✓ The principal chemical instability of the cephalosporins is associated with β-lactam bond hydrolysis.
- ✓ Cephalosporins with 3-acetoxymethyl group undergo solvolysis (hydrolysis) in strongly acidic solutions forming desacetylcephalosporin derivatives that lactonize to inactive lactones (that masks COOH group).
- ✓ The 7-acylamino group of some cephalosporins can also be hydrolyzed under enzymatic (acylases) and non-enzymatic conditions to give 7-ACA (or 7-ADCA) derivatives. Following hydrolysis of the 3-acetoxymethyl group and lactonization under acidic conditions.



2- Effect of β-Lactamases

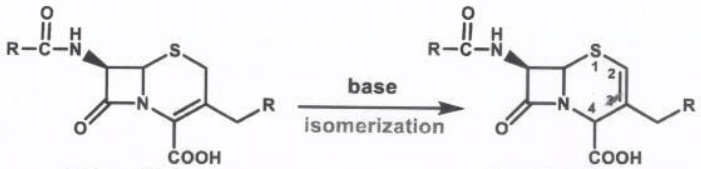
✓ Susceptible cephalosporins can be hydrolyzed by β-lactamases before they reach the penicillin-binding proteins





3- Effect of mild base on cephalosporin

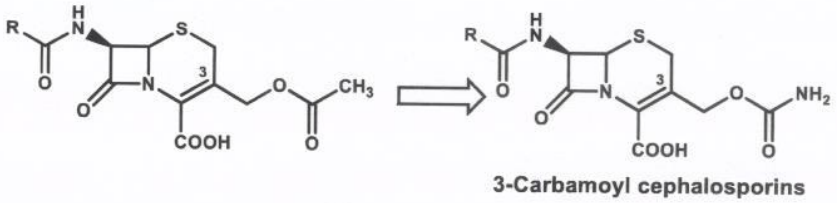
✓ Isomerization of the olefinic linkage to C-3,4 leads to great losses in antibiotic activity.



Chemical modification to inhibit lactonization

✓ Cephalosporins lacking this hydrolysable group are not subject to hydrolysis by esterases and hence not subject to in vivo inactivation .

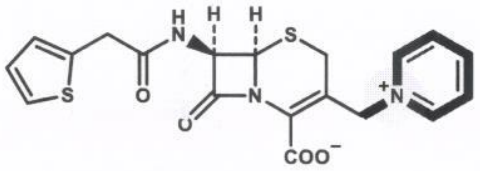
1. Carbamoyl cephalosporins:



✓ Replacing the CH_3 gr of an ethanoate ester with NH_2 results in a urethane functional gr which is more stable than the original ester.

- Low plasma protein binding (ppb): short half-life.

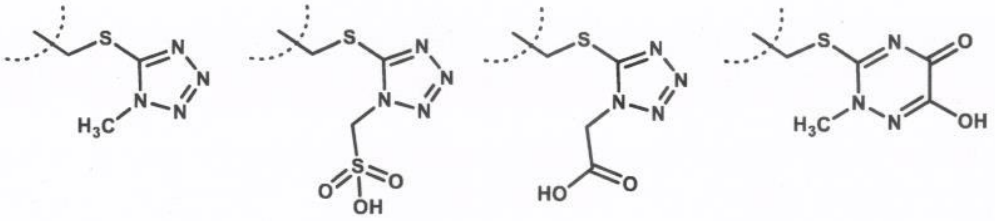
2. 3-Pyridiniummethyl cephalosporins:



Cephaloridine

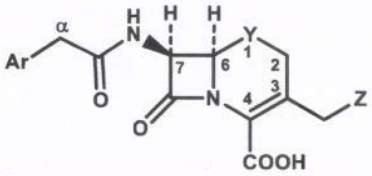
- ✓ Replacing the ester with a metabolically stable pyridinium group gives cephaloridine.
- ✓ Yet, it is not suitable for oral administration as it is liable to acid hydrolysis.

3. **3-[(Heterocyclo)thio]methyl cephalosporins:**



4. **3-H, 3-CH_3, 3-vinyl or 3-Cl:**
   - ✓ Derivatives carrying one of the above functions are suitable for oral administration.

SAR of cephalosporin



1. β-lactam ring within the bicyclic system is essential for activity.
2. When Y = S → Greater antibacterial activity than if Y = O.
3. Double bond at C-3 is essential, its shifting to 2 or saturation give inactive product.
4. Ionized (free) COOH group at C-4 is essential for activity.
5. The 6α-H is essential for biologic activity.
6. The 7β-amino group is essential for antimicrobial activity.
7. Replacement of 7α-H with 7α-OCH_3 improves the antibacterial activity and stability toward β-lactamase.
8. The addition of $-NH_2$ to the α position in the acyl side → improves acid (and hence oral) stability of the β-lactam of the cephalosporin.

Generations of Cephalosporins

1. **The first generation cephalosporins**
   - ✓ They are primarily active against Gram (+) bacteria.

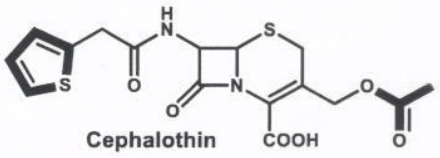
- ✓ They are not effective against methicillin-resistant *Staph. aureus*.
- ✓ They are not significantly active against Gram (-) bacteria.

2. **The second generation cephalosporins**
   - ✓ They generally retain the anti-Gram (+) activity and add better antiGram (-) activity.
3. **The third generation cephalosporins**
   - ✓ They are less active against *staphylococci* than the first-generation agents but are much more active against Gram (-) bacteria than either the first or the second-generation drugs.
4. **The fourth generation cephalosporins**
   - ✓ They have an antibacterial spectrum like the third-generation drugs but add *Pseudomonas aeruginosa* and some enterobacteria that are resistant to the third-generation cephalosporins.
   - ✓ They are also more active against some Gram (+) organisms.
5. **The fifth generation cephalosporins**

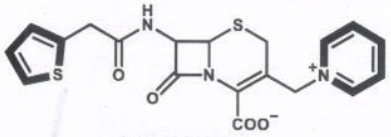
The first generation cephalosporins

Parentral agents

❋ **Cephalothin**



Cephalothin



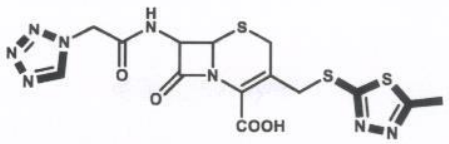
Cephaloridine

- ✓ Cephalothin (Cefalotin) has relatively short duration of action.
- ✓ The acetyloxy group is important to the mechanism of inhibition and acts as a good leaving group.

❋ **Cephaloridine**

- ✓ Cephaloridine exists as a zwitterion and is water soluble, but it is poorly absorbed through the gut wall and has to be injected.

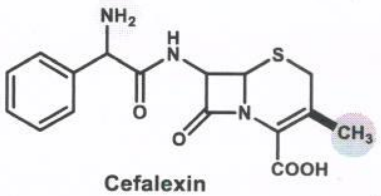
❋ **Cefazolin**



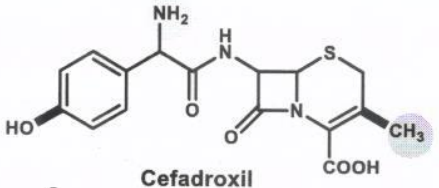
Cefazolin or cephazolin

- ✓ It also contains unusual tetrazolylacetyl acylating group

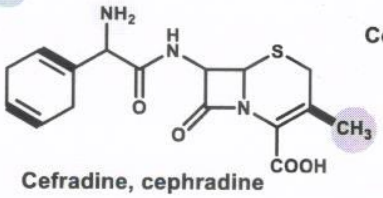
Oral agents



Cefalexin



Cefadroxil

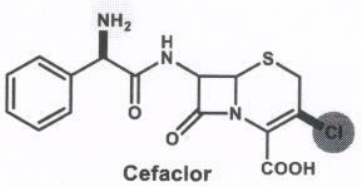


Cefradine, cephradine

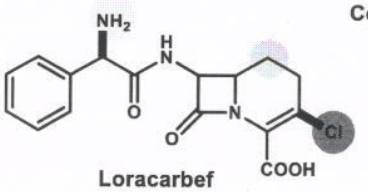
- ✓ They have a 3-CH_3 group which help oral absorption but it is bad for activity as it is not a good leaving group.
- ✓ However, the presence of a hydrophilic amino group at the α-carbon of the 7-acylamino side chain helps to restore the activity.
- ✓ ***Properties:***
  - Excellent oral activity, why?
  - Broad spectrum activity (G +ve) & some Gram-negative bacilli.
  - Poor β-lactamase stability.
  - Poor ability to penetrate cerebrospinal fluids.
  - Lack activity against *Pseudomonas aeruginosa*.

1- The second generation cephalosporins

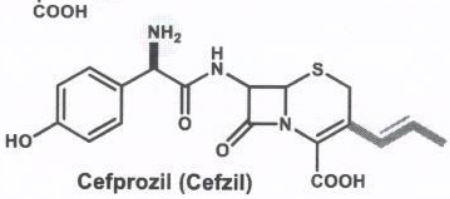
Oral agents



Cefaclor



Loracarbef



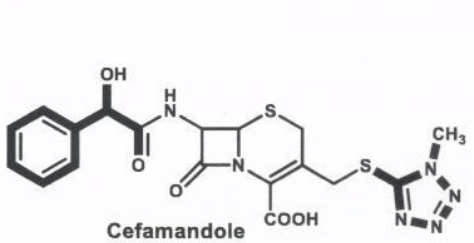
Cefprozil (Cefzil)

- ✓ **Cefaclor** is less active against Gram-negative bacteria than the other second-generation cephalosporins but is more active against gram-negative bacteria than the first-generation drugs, Why?
- ✓ **Cefprozil** it has a l-propenyl group conjugated with the double bond in the six-membered ring

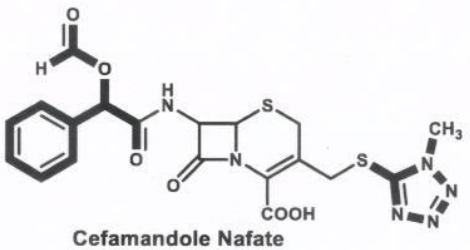
- ✓ **Loracarbef** (it is a ***carbacephem***) is a synthetic more chemically stable, "carba" analog of cefaclor, with similar pharmacokinetic and microbiological properties.

Parentral agents

Cefamandol and Cefamandole nafate



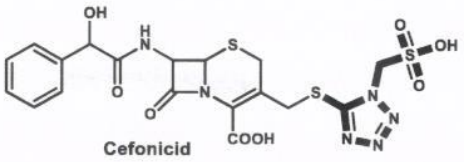
Cefamandole



Cefamandole Nafate

- ✓ They have D-mandelic acid (D-α-Hydroxybenzyl) as the acyl portion.
- ✓ Cefamandole nafate is the formate ester of cefamandole.
- ✓ Esterification of the α-OH group of the D-mandeloyl function overcomes the instability of cefamandole in solid-state dosage forms, and provides satisfactory concentrations of the parent antibiotic in vivo through spontaneous hydrolysis of the ester at neutral to alkaline pH to release cefamandole and formate.
- ✓ As the antibiotic is broken down in the body, it releases free N-methyl-5-thiotetrazole (MTT) which can cause hypoprothrombinemia
- ✓ Cephalosporins containing an N-methyl-5-thiotetrazole (MTT) moiety at the 3-position (e.g., cefamandole, cefotetan, cefmetazole, moxalactam, and cefoperazone) have been implicated in a higher incidence of hypoprothrombinemia than cephalosporins lacking the MTT group. This effect is enhanced and can lead to severe bleeding in patients with poor nutritional status, debilitation, recent GI surgery, hepatic disease, or renal failure.
- ✓ Treatment with vitamin K restores prothrombin time to normal in patients treated with MTT-containing cephalosporins.
- ✓ The MTT group has also been implicated in the intolerance to alcohol Thus, disulfiram-like reactions, attributed to the accumulation of acetaldehyde and resulting from the inhibition of aldehyde dehydrogenase–catalyzed oxidation of ethanol by MTT-containing cephalosporins, may occur in patients who have consumed alcohol before, during, or shortly after the course of therapy.

Cefonicid



Cefonicid

- ✓ Cefonicid is structurally similar to cefamandole, except that it contains a methane sulfonic acid group attached to the N-1 position of the tetrazole ring (instead of CH_3).
- ✓ Cefonicid is associated with hypoprothrombinemia, True/False???

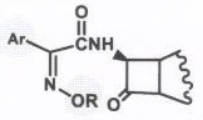
Parenteral and β-lactamase stable agents

Three structural features confer broadly based resistance to β-lactamases among the cephalosporins:

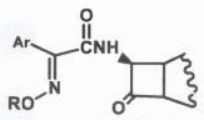
1- **7α-Methoxy group → Cephamycins.**

2- **Alkoximino function (=N-OR) in the aminoacyl group.**

- ✓ Both steric and electronic properties of the alkoximino group contribute to the β-lactamase resistance conferred by this functionality since *syn*-isomers (Z-oxime) are more active than *anti*-isomer (E-oxime).



syn-Oxime



anti-Oxime

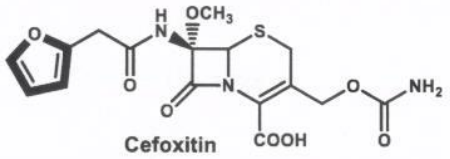
3- **3. Acylureidocephalosporin (e.g. cefoperazone):** that contains the same group present in piperacillin (4-ethyl-2,3-dioxo-1-piperazinylcarbonyl: Steric factors).

A. Cephamycin C Modifications

Cephamycin C

- ✓ Cephamycins have broader spectrum of activity than most first-generation cephalosporins
- ✓ This is due to greater resistance to β-lactamase enzymes, which may be due to the steric hindrance provided by the 7α-methoxy group.
- ✓ The parent compound cephamycin C was isolated from a culture of *Streptomyces clavuligerus* and was the first β-lactam to be isolated from a bacterial source.

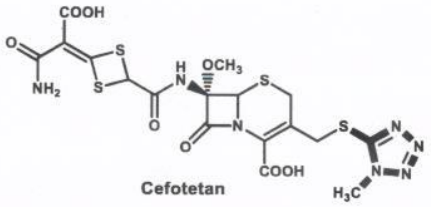
❋ **Cefoxitin**



Cefoxitin

- ✓ Modification of the sidechain of cephamycin C gave cefoxitin.
- ✓ It shows good metabolic stability to esterases.
- ✓ Poor absorption through the gut wall and therefore administered by injection.

❋ **Cefotetan**



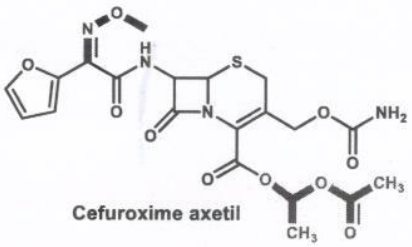
Cefotetan

- ✓ It has unusual sulfur-containing C-7 side-chain amide.
- ✓ It contains the MTT group that has been associated with hypoprothrombinemia and alcohol intolerance*.

B. Oximinocephalosporins

❋ **Cefuroxime**

Cefuroxime



Cefuroxime axetil

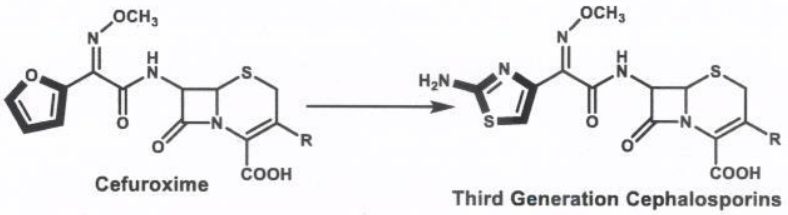
- ✓ It has A *syn* (Z) methoxyimino substituent is associated with β-lactamases stability result from its steric effect.
- ✓ Poor activity against *Pseudomomnas aeruginosa*.

Cefuroxime axetil

- ✓ It is 1-[acetyoxy]ethyl ester prodrug of cefuroxime.
- ✓ During absorption, this acid-stable, lipophilic, oral prodrug is hydrolyzed to cefuroxime by intestinal and/or plasma enzymes

2- The third generation cephalosporins

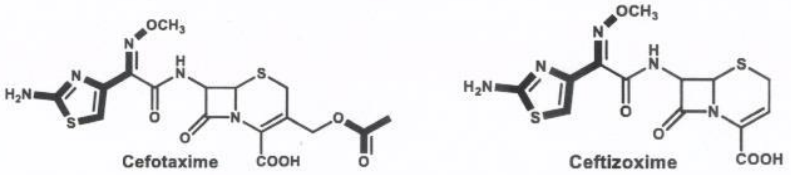
✓ Replacing the furan ring of the Cefuroxime with an aminothiazole ring.



✓ As a result, third-generation cephalosporins containing this ring have a marked increase in activity against Gram-negative bacteria.

Parenteral agents

❋ **Cefotaxime**



✓ Cefotaxime has a metabolically vulnerable acetoxy group attached to C-3 and loses about 90% of its activity when this is hydrolyzed.

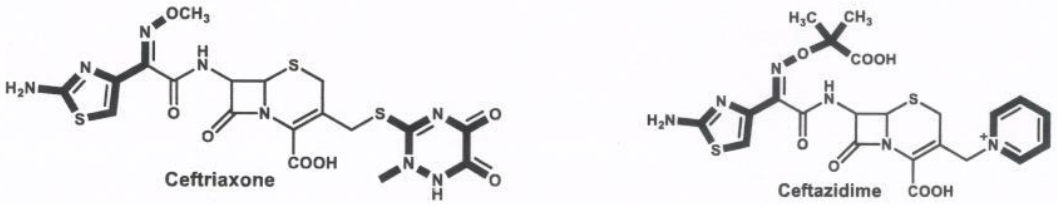
❋ **Ceftizoxime**

✓ The whole C-3 side chain has been omitted to prevent deactivation by hydrolysis.

✓ It is not metabolized in vivo so it is excreted largely unchanged in the urine.

✓ Cefotaxime and Ceftizoxime have Greater anti–*Pseudomonas aeruginosa* activity.

❋ **Ceftriaxone**



✓ It has metabolically stable, activating and highly acidic thiotriazinedione at C-3.

✓ It is 95% serum bound and exhibits an extended serum profile making it suitable for once daily administration.

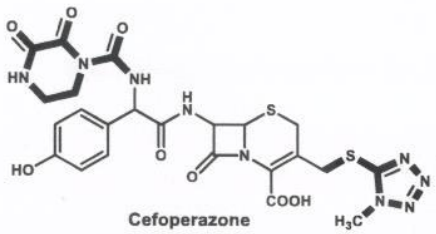
✓ Greater anti–*Pseudomonas aeruginosa* activity.

❋ **Ceftazidime**

✓ The C-3 side chain was replaced by a charged pyridinium moiety.

✓ The oxime moiety has a polar function (2-methylpropionic acid) group.

❋ **Acylureidocephalosporin, Cefoperazone**

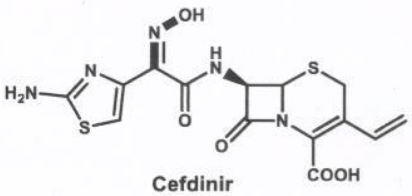


Cefoperazone

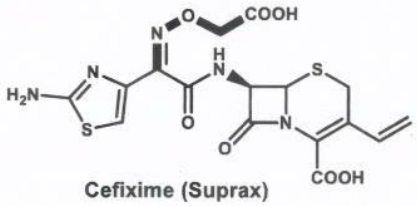
- ✓ The uridoacyl-derived cephalosporin with: -
- ✓ It contains the MTT group that has been associated with hypoprothrombinemia and alcohol intolerance.

Oral agents

❋ **Cefdinir**



Cefdinir

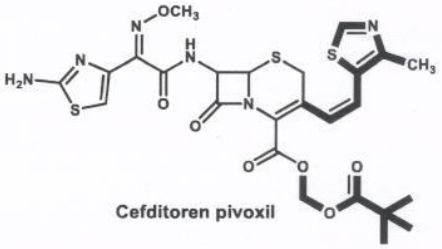


Cefixime (Suprax)

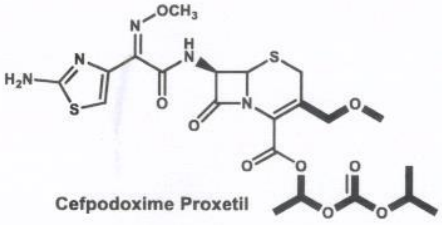
- ✓ Vinyl group at C3 → oral activity.
- ✓ Resistance to β-lactamases.

❋ **Cefixime:** Z-oximino acidic ether at C-7 → enhanced β-lactamase stability.

❋ **Cefditoren and Cefditoren pivoxil**



Cefditoren pivoxil



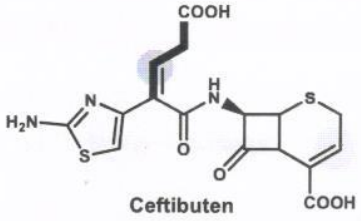
Cefpodoxime Proxetil

- ✓ It is an orally active drug and can be formulated as the prodrug cefditoren pivoxil.

❋ **Cefpodoxime proxetil.**

- ✓ It is the isopropyloxycarbonylethyl ester of cefpodoxime.

❋ **Ceftibuten**

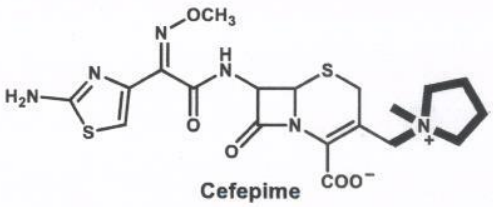


Ceftibuten

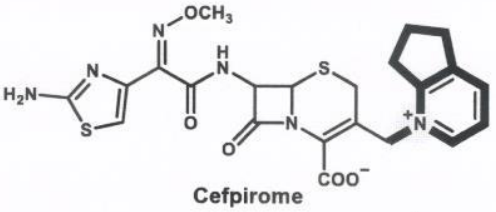
- ✓ It has a Z-olefinic methylene group (C=CHCH₂-) (Z-ethylidinecarboxyl group).
- ✓ Enhanced β-lactamase stability and chemical stability.

3- The fourth generation cephalosporins

❋ Cefepime and Cefpirome



Cefepime

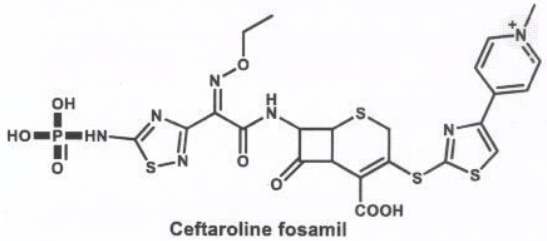


Cefpirome

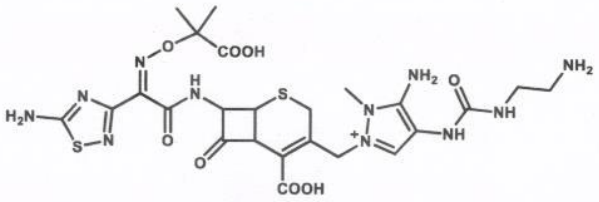
- ✓ They contain Z-methoxyimine moiety & aminothiazolyl group at C-7 in addition to quaternary ammonium group at C-3* and hence are zwitterionic compounds.

4- The Fifth generation cephalosporins

❋ Ceftaroline fosamil



Ceftaroline fosamil



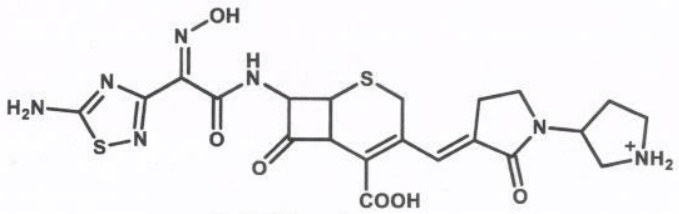
Ceftolozane

- ✓ It has activity against various strains of methicillin-resistant Staphylococcus aureus (MRSA) and multi-resistant Streptococcus pneumonia (MDRSP).
- ✓ It acts as a prodrug for ceftaroline.

❋ Ceftolozane

- ✓ Ceftolozane was developed for the treatment of infections with gram-negative bacteria that have become resistant to conventional antibiotics.
- ✓ It is combined with the β-lactamase inhibitor tazobactam.

❋ Ceftobiprole



Ceftobiprole

- ✓ Ceftobiprole it is effective against (MRSA) and (MDRSP) soused for the treatment of hospital and community-acquired pneumonia and community-acquired pneumonia.